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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
31 October 2002 (31.10.2002)

PCT

(10) International Publication Number
WO 02/085337 A1(51) International Patent Classification?: **A61K 9/51**(21) International Application Number: **PCT/CA02/00542**(22) International Filing Date: **22 April 2002 (22.04.2002)**(25) Filing Language: **English**(26) Publication Language: **English**(30) Priority Data:
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(CA).(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VN, YU, ZA, ZM, ZW.(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG).**Published:**

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/085337 A1

(54) Title: **MICELLAR DRUG DELIVERY SYSTEMS FOR HYDROPHOBIC DRUGS**

(57) Abstract: This invention provides compositions comprising a hydrophobic drug, a biocompatible micelle forming polymer, and a biocompatible low molecular weight, water-soluble polymer. Also provided are devices for injection of such compositions and for the use of such compositions to form hydrophobic drug containing micelles within the body of a patient.

Micellar Drug Delivery Systems for Hydrophobic Drugs

Field of the Invention

This invention relates to micellar compositions for drug formulation and drug delivery.

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Background of the Invention

There are a large number of therapeutic compounds that, due to poor water solubility, will not dissolve well in aqueous pharmaceutical carriers (making administration difficult) and exhibit poor availability. One solution has been to reformulate such drugs as water-soluble derivatives. This approach often yields compounds with less efficacy than the parent compound.

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Another solution has been to incorporate hydrophobic drugs into micelles. Such micellar formulations are expected to achieve some level of circulation concentration of the drug without precipitation of the drug in the bloodstream. The principle behind micelle formation is that amphipathic molecules can form aggregates in an aqueous environment whereby hydrophobic components of the molecules come together to exclude water and make up the inner core of the micelle. The hydrophilic components of the molecules are orientated towards the outside of the micelle. This aggregation occurs above the critical micelle concentration (CMC) of the molecules in water. Under careful conditions, hydrophobic drugs may be solubilized in the inner hydrophobic core of micelles during their formation. These micellar formulations are utilized almost exclusively for the systemic administration of drugs and are usually delivered intravenously or intraperitoneally, but have also been suggested for oral administration.

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The literature describes numerous methods to incorporate hydrophobic drugs such as methotrexate, indomethacin, paclitaxel and doxorubicin into micelles made from biocompatible, amphipathic polymeric molecules (e.g. US patent 6,322,805; Kim SY et al. J. Controlled Release (1998) 56:13-22; Inoue T et al. J. Controlled Release (1998) 51:221; and, Kataoka K. J. Controlled Release (2000) 64:143-153). While the literature does describe formation of hydrophobic drug containing micelles with the hydrophobic drug and a micelle forming polymer being in aqueous solution during vigorous agitation

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or sonication of the solution, the amount of drug loading is poor as a result of its low solubility. Thus, micellar compositions are typically made by dissolving a hydrophobic drug in a water miscible organic solvent in which the drug is soluble, combining the resulting solution with a micellar composition in an aqueous solution with mixing by
5 vigorous stirring, agitation, or sonication. For example, the mixture might be stirred for up to about 24 hours and any remaining drug not incorporated into micelles then removed. The resulting micellar solution may then be used directly for administration or freeze-dried into nanoparticles (which may be resuspended in water at a later time) providing the solvent is biocompatible and/or is capable of being removed by freeze-
10 drying or other methods. These methods are complicated, expensive, and expose potentially water labile drugs to long periods in aqueous media. In addition there is a need to remove the organic solvent, which is often not pharmaceutically compatible or desirable.

15 One process for removal of an organic solvent is by solvent evaporation. In this method, a hydrophobic drug is typically dissolved in a water-miscible organic solvent and introduced to an aqueous solution of micelles. Subsequently, the organic solvent is evaporated off at elevated temperature. Alternatively, the drug and a micelle forming polymer are both dissolved in an organic solvent and the solvent is evaporated at elevated
20 temperature. The resulting mixture is kept at an elevated temperature while warm water or aqueous solution is added with vigorous stirring until polymeric micelles containing the drug are formed. Also a dialysis method can be used, where a suitable water-miscible organic solvent is used to dissolve the hydrophobic drug and the micelle forming polymer. The solution is subsequently dialysed against a buffer solution and then against
25 water. In some cases the duration of dialysis may be as long as 72 hours (Yu B.G. et al. J Controlled Release (1998) 56:285-291).

US patent 4,745,160 (Churchill J.R. et al.) teaches a process for manufacturing micelle compositions from biodegradable amphipathic copolymers. The patent teaches that in
30 order to incorporate a hydrophobic drug it is necessary to dissolve the drug in a water miscible organic solvent such as dioxan, acetic acid, acetonitrile, methanol or ethanol.

US patent 5,510,103 (Yokoyama M. et al.) and US patent 5,939,453 (Heller J. et al.) describe micelles made of block copolymers in which hydrophobic drugs are physically trapped. However, the disclosed methods of trapping require heating, ultrasonication, and/or the use of organic solvents and dialysis.

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US patent 6,136,846 (Rubinfeld J. et al.) describes incorporation of paclitaxel into micelles made from amphipathic block copolymers in which the hydrophobic block is a lipid tail. Organic solvents are used but the patent also teaches that polyethylene glycol (PEG) of 300-400 molecular weight may be used as the "solubilizer". Paclitaxel loading of about 2% is reported in the examples set out in the patent.

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Zhang X. et al. (Int'l. J. Pharmaceutics (1996) 132:195-206) reports the formation of a matrix containing taxol and a diblock copolymer composed of methoxy polyethylene glycol (MePEG) and polylactic acid. Only if the matrix is made with acetonitrile as an organic solvent, will the resulting matrix be capable of forming micelles following evaporation of the solvent. The resulting matrix must be heated to melt the polymer and vigorously agitated in aqueous medium in order to produce drug containing micelles.

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In WO9921908, Zhang, X. et al., teaches the production of a semi-solid polymer mixture comprising hydrophobic drug, a water soluble polymer such as MePEG, and a hydrophobic polymer. It was found that the hydrophobic drug precipitates in the mixture thereby solidifying the material.

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Summary of the Invention

This invention provides micellar compositions for improved hydrophobic drug loading and compositions comprising hydrophobic drugs capable of forming drug containing micelles which may be made without a non-polymeric organic solvent and without heating or agitation. This invention allows for the formulation and non-oral administration by injection of semi-solid mixtures into the body of a patient whereby the semi-solid material spontaneously forms micelles containing the hydrophobic drug which enter the bloodstream.

- 10 In one aspect, the present invention provides for improved hydrophobic drug loading into micelles by using selected amphipathic diblock copolymers including those described by Zhang et al. (1996), without an organic solvent such as acetonitrile being required. The micelles are formed from a micelle forming composition comprising a biocompatible, low molecular weight, water soluble polymer (including the PEG "solubilizer" taught in US
- 15 6,136,846 and the micelle forming compositions of this aspect of the invention exhibit low critical micelle concentrations (CMC) under about 500 μ M to as low as about 20 μ M as determined by standard techniques). Hydrophobic drug loading using this aspect of the invention can achieve drug levels in the micellar composition in excess of 10% (by weight) and as high as about 25% when the CMC is about 50 μ M or less. This is
- 20 surprising because Zhang et al. (1996) found such diblock copolymer formulations required acetonitrile to adequately distribute taxol in a matrix in order for micelles to be produced from the matrix. WO9921908 suggests that making a polymeric composition comprising a free water soluble polymer and a hydrophobic drug will result in precipitation of the drug, which is counter-productive to the production of micelles.
- 25 Further, Zhang et al. (1996) suggests that increasing amounts of a water soluble polymer (MePEG) in a matrix results in less efficient micelle production from the matrix and poor distribution of the drug in the matrix.

This aspect of the invention provides a micelle forming composition comprising:

- 30 (a) one or more hydrophobic drugs;
- (b) one or more biocompatible, micelle forming polymers; and,

(c) one or more biocompatible, low molecular weight, water soluble polymers, wherein the micelle forming polymer is a copolymer comprising a hydrophobic and a hydrophilic portion, the hydrophobic portion being selected from the group consisting of: a polyester and a polyanhydride; and, the hydrophilic portion is a polyethylene oxide having a molecular weight of about 750 or more. Also provided are micelles formed from the aforementioned composition.

A second aspect of the invention results from the discovery that a micellar composition comprising a biocompatible micelle forming polymer; a biocompatible, low molecular weight water soluble polymer; and, a hydrophobic drug, may be formulated as a semi-solid material (e.g. a wax like substance or a paste) capable of being injected into a patient and which will spontaneously form drug containing micelles at the site of deposition of the material in the patient. The water soluble polymer may be one that is liquid or semi-solid at about room temperature (e.g. at about 20-30° C). Once the material has been injected into a patient or is simply placed in an aqueous solution, it will form hydrophobic drug containing micelles without the need for heating or agitation. This aspect of the invention has the advantage of providing short to medium term localization of a drug at a specific site of injection in a patient, with the drug being released inside micelles to the physiological environment of the site and ultimately to the bloodstream. This aspect of the invention includes compositions comprising a hydrophobic drug, a biocompatible micelle forming polymer and a sufficient amount of a biocompatible low molecular weight water soluble polymer such that the composition is a semi-solid (e.g. a "paste") at temperatures at or about room temperature and is injectable through a syringe.

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This aspect of the invention provides a micelle forming composition comprising:

- (a) one or more hydrophobic drugs;
- (b) one or more biocompatible, micelle forming polymers; and,
- (c) one or more biocompatible, low molecular weight, water soluble polymers, wherein the one or more water soluble polymers are present in an amount sufficient that the composition is injectable.

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This invention also provides methods for using the aforementioned compositions to form micelles *in vitro* and *in vivo*. *In vivo* methodologies include injection of the composition to a site in a patient's body where drug containing micelles are formed at the site.

- 5 This invention also provides injection devices such as a syringe containing a micelle forming composition according to this invention.

Brief Description of the Figures

Figure 1 is a graph showing size distribution micelles with a peak at a particle size diameter of approximately 10nm. Size distribution was measured on a Zetasizer 3000HS at a temperature of 25 C, at a count rate of 12.0 kCps, with a detector angle of 90.00 and at a wavelength of 633.0.

Detailed description of the invention

In the description that follows, a number of terms are used extensively, the following definitions are provided to facilitate understanding of the invention.

"Micelle forming polymer" as used herein refers to an amphipathic polymer that is comprised of both a hydrophilic and a hydrophobic component and which is capable of forming micelles in water. Numerous examples are known and are disclosed in the art. Micelle forming polymers include block (e.g. diblock) copolymers comprising a hydrophobic block and a hydrophilic block such as are disclosed in the prior art documents referred to above and in WO01/87345. The micelle forming polymers known in the art that are employed in this invention are those that are biocompatible and thus pharmaceutically suitable. Such is the case for the specific polymers disclosed herein.

As used herein, a "hydrophobic drug," is a water insoluble drug. A "drug" is a therapeutically active substance which is delivered to a living subject to produce a desired effect, such as to treat a condition of the subject. A drug is also provided to a subject prophylactically to prevent the development of a condition or to decrease the severity of a condition that the subject may develop. A "water insoluble drug" has a solubility of less than 0.1 mg/mL in distilled water at 25°C. Within the context of the present invention, a "slightly soluble drug" (solubility: 1-10 mg/mL) and a "very slightly soluble drug" (solubility: 0.1-1 mg/mL) may also be referred to. These terms are well-known to those of skill in the art. See, e.g., Martin (ed.), Physical Pharmacy, Fourth Edition, page 213 (Lea and Febiger 1993). Examples of hydrophobic drugs include the following agents including their water soluble derivatives and analogs:

(a) Amphotericin: used for the treatment or prevention of infection of an open wound by topical administration or for the treatment or prevention of an infection in an exposed

wound after surgery by local application. Amphotericin is an antifungal and is insoluble in water at pH 6 to 7 (The Merck Index.).

(b) Anthralin: used for the treatment of "wet" psoriasis by topical application.

Anthralin is an agent for psoriasis therapy and is practically insoluble in water (The

5 Merck Index).

(c) Beclomethasone: used for the reduction of local inflammation by peri-ophthalmic and inside the eyelid or intranasal (e.g., for the treatment of rhinitis) application.

Beclomethasone is a corticosteroid and is very slightly soluble in water. See, for example, Gennaro, (ed.), Remington's Pharmaceutical Sciences. I 7th Edition, (Mack

10 Publishing Company 1985).

(d) Betamethasone: used for the reduction of local inflammation by oral (e.g., canker sore), intravaginal, and intrarectal application. Betamethasone is a corticosteroid and has a solubility of 190 µg/mL water. See, for example, Gennaro, (ed.), Remington's Pharmaceutical Sciences, 17th Edition, (Mack Publishing Company 1985).

15 (e) Camptothecin: used for the treatment of diseases involving cellular proliferation such as cancer, arthritis, psoriasis, restenosis, surgical adhesions. Camptothecin has a water solubility of 1-2 µg/mL.

(f) Curcumin: a potent antioxidant and potential antiarthritic drug. Curcumin is practically insoluble in water.

20 (g) Dexamethasone: used for the reduction of local inflammation by oral application (e.g., post wisdom tooth removal). Dexamethasone is a corticosteroid and has a solubility of 10 µg/mL in water (The Merck Index).

(h) Genistein: a tyrosine kinase inhibitor and potentially used for the treatment of diseases involving cellular proliferation. Genistein is practically insoluble in water.

25 (i) Indomethacin: used for the treatment of symptoms of gout by intraarticular or intramuscular injection or for the reduction of local inflammation by peri-ophthalmic and inside the eyelid, oral, intranasal, intravaginal and intrarectal application. Indomethacin is a non-steroidal anti-inflammatory (NSAID) and is practically insoluble in water (The Merck Index).

30 (j) Lidocaine: provides local anesthesia by intramuscular injection, or administration by application to mucus membranes, including periophthalmic and inside the eyelid, oral, intranasal, intravaginal and intrarectal. Lidocaine is a local anesthetic and is practically

insoluble in water. See, for example, Gennaro, (ed.), Remington's Pharmaceutical Sciences, 17th Edition, (Mack Publishing Company 1985).

(k) Taxol (e.g. Paclitaxel): used for the treatment of angiogenic related diseases such as arthritis, cancer, restenosis, psoriasis, or surgical adhesions. Paclitaxel has a water
5 solubility of 1-2 , $\mu\text{g/mL}$.

(l) Tetracycline: used for the treatment of eye infections by periophthalmic and inside the eyelid application. Tetracycline is an antibacterial and has a solubility of 400 pg/mL water. See, e.g., Gennaro, (ed.), Remington 's Pharmaceutical Sciences, 17th Edition, (Mack Publishing Company 1985).

10 (m) Tretinoin: a retinoic acid that is potentially an anticancer agent. Tretinoin is practically insoluble in water.

(n) Therapeutic proteins: proteins that are practically insoluble in water, such as insulin, are contemplated for use in this presently described polymeric drug delivery system.

15

The present invention does not require the use of an organic solvent as traditionally used for dissolving a hydrophobic drug during preparation of drug containing micelles. The term "organic solvent" as used herein with reference to this invention means a non-polymeric solvent, such as an aromatic hydrocarbon, ester, ether, ketone, amine, alcohol,
20 nitrated hydrocarbon and chlorinated hydrocarbon, which non-polymeric solvents include: acetone, ethanol, tetrahydrofuran, acetonitrile and pyrrolidones. Some of these organic solvents are not biocompatible and organic solvents are not suitable for injection into various areas of the patient's body, particularly the eye, blood vessels, or the synovial joint.

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This invention makes use of a biocompatible, low molecular weight, water soluble polymer in place of an organic solvent as defined above. This obviates the need to remove an organic solvent and permits the formation of hydrophobic drug containing micelles without heating, agitation, vigorous stirring or sonication. It also makes possible
30 the preparation of a semi-solid capable of forming micelles *in vivo*, for administration by injection to a patient.

The term "injectable" as used herein refers to compositions having a viscosity that permits injection of the material into the body of a patient using a syringe and a needle cannula with the amount of pressure required to inject the material being that which may be comfortably exerted through hand pressure. Material having viscosities between about 5
5 and about 200 poise which may be measured using known techniques (for example with a parallel plate rheometer). Material that is injectable according to this invention is injectable in a typical temperature range for injection. Preferably, the material is injectable from about room temperature to about body temperature. Most preferably, the material is injectable in a temperature range from about 20° C to about 40° C.

10

The terms "substantially free of..." or "containing substantially no..." with reference to a possible ingredient in a composition means that the composition comprises none, or essentially none of the ingredient. By this definition, the ingredient may be present in such small amounts in the composition that do not affect the properties or pharmaceutical
15 utility of the composition.

Micelle forming compositions according to this invention may be prepared using standard techniques whereby the required polymeric ingredients and a hydrophobic drug are thoroughly mixed or intermingled. Mechanical mixing procedures may be employed,
20 such as are taught in the Examples below. The goal is to achieve a thorough blending of the ingredients of the composition.

Injection devices such as syringes may be prepared so as to contain micelle forming compositions of this invention by using any technique whereby the composition is placed
25 within the injection device in a manner that the composition becomes injectable by the device. For example, a composition of this invention may be placed within the barrel of a syringe by mechanical means or extrusion.

Compositions of this invention may be stored for substantial lengths of time. When a
30 hydrophobic drug is present in a composition of this invention, it is preferred that the composition be stored at a temperature below that of room temperature in accordance with the stability parameters of the selected drug.

Compositions of this invention may be placed in sterile containers for subsequent pharmaceutical formulation. Such a container may be a sealed vial which preferably will contain sufficient space for the subsequent addition of an aqueous, physiologically acceptable carrier. Thus, the compositions of this invention may be employed for production of drug containing micelles within the aforementioned container after introduction of the aqueous carrier. Dissolution of the composition in the carrier with concomitant formation of drug containing micelles may be accelerated by agitation (e.g. shaking) although the compositions of this invention will dissolve over time, without agitation. Long term or vigorous agitation or sonication is not necessary.

Methods for administration of compositions according to this invention and drug containing micellar suspensions made from such compositions may be done according to methods known in the art. Methodologies for injection of such compositions or solutions at a selected site within the body of a patient may be selected and performed by a medical professional.

For injectable compositions of this invention, the composition will comprise one or more biocompatible micelle forming polymers. Such micelle forming polymers may be any such polymer known in the art, including the references referred to above and in WO 01/87345. Preferably, one or more micelle forming polymers in compositions of this invention will be a diblock copolymer suitable for formation of micelles as taught in the art or as specifically described herein. Hydrophobic portions of such diblock copolymers may comprise one or more hydrophobic polymers, such as polyesters, polyanhydrides, polyglycolic acids, polybutyrolactones, polyhydroxybutyrates, polylactic acids and polylacapolactones. The hydrophobic portion of the copolymer may comprise one or more different hydrophobic polymers in random or block orientation. Preferably, the hydrophobic portion of a copolymer will have a molecular weight from about 200 to about 5000.

The preferred micelle forming polymers described above are capable of forming micelles at very low critical micelle concentrations (CMC), which allows for loading of high concentrations of hydrophobic drugs.

- 5 Preferred hydrophilic portions of micelle forming copolymers that may be used in this invention have a molecular weight of about 750 or greater up to about 8000. Preferably, the molecular weight will be in the range of about 1000 or 2000 - 3000 or 5000. Most preferred is a molecular weight of polymer as the hydrophilic portion of the micelle forming polymer being about 2000.

10

Biocompatible water soluble polymers for use in this invention include any suitable water soluble polymer capable of fluidizing a micelle forming polymer as used in this invention. Such water soluble polymers include pluronics that is a liquid or solid at room temperature, or low molecular weight polyesters such as glycolitic or lactic acid
15 polymers of sufficiently low molecular weight that the polymer is a liquid or semi-solid at room temperature (e.g. about 20 to 30° C). Preferred water soluble polymers for use in this invention are polyethylene oxides of a molecular weight of about 1000 or less, including PEG and MePEG.

- 20 Weight ratios of hydrophobic and hydrophilic components of micelle forming polymers used in this invention may be adjusted to provide for a desired CMC. The amount of water soluble polymer employed in compositions of this invention may be adjusted to achieve a desired consistency of the resulting mixture of matrix. For injection, it is preferred that the amount of water soluble polymer be such that the
25 resulting mixture or matrix is injectable, as defined herein. The amount of hydrophobic drug included in the composition will be such as to provide a desired amount of drug loaded micelles, preferably not exceeding an amount that can be sufficiently distributed within the micelle forming composition.

30

Example 1**Manufacture of diblock copolymer**

5 Methoxypolyethylene glycol (MePEG) oligomers of molecular weight 750 and 2000 and stannous octoate were obtained from Sigma-Aldrich (St. Louis, MO), while ϵ -Caprolactone was obtained from Aldrich (Milwaukee, WI). Chloroform and dichloromethane (DCM) were HPLC grade (Fisher Scientific, Fair Lawn, NJ).

10 Copolymers of methoxypolyethylene glycol (MePEG) and poly(ϵ -caprolactone) were prepared as follows. MePEG oligomers with molecular weights of 750 and 2000 were combined with ϵ -caprolactone in varying weight ratios to control the final molecular weight of the copolymer. The total weight of the two reagents was 50 g. The reagents were placed in a round bottom flask sealed with a ground glass stopper and immersed in a heavy mineral oil bath heated to 140°C. The temperature was controlled using a Dyna-
15 Sense MK-1 controller (Scientific Instruments Inc., Skokie, IL). The reagents were stirred using a teflon coated 2.5 cm magnetic stir bar. After the reagents were mixed for 30 minutes to produce a homogeneous liquid, 0.15 ml of stannous octoate was added to the flask. The polymerization reaction was allowed to proceed for 6 hours. Cooling the polymer to room temperature terminated the reaction.

20

Example 2A**Manufacture of a micellar formulation of paclitaxel**

25 Fifty mg of paclitaxel (Hauser chemicals), 380 mg of methoxypolyethylene glycol (MePEG) (molecular weight 350) (Union Carbide Inc.) and 570 mg of poly-L-lactic acid-MePEG diblock copolymer (Angiotech Pharmaceuticals, Vancouver Canada) were weighed into a 20 ml glass vial and stirred at 50°C using a spatula. The mixture formed a miscible composition in which all the drug was dissolved. The mixture was sucked up into a 1 ml syringe through an 18 gauge needle and allowed to cool to room temperature.

30

The waxy material could be injected easily through a 21-gauge needle without compromise of the integrity of the composition. When 100 μ l of the mixture was injected

into 5 ml of water the mixture slowly dissolved. There was no precipitation of any of the components. The formulation self assembled into micelles with a particle size of approximately 10nm diameter, as shown in **Figure 1**. This solution had a paclitaxel concentration of 1 mg/ml, almost 1000 fold greater than the free solubility of the drug in water.

Example 2B

Manufacture of alternate micellar formulation of paclitaxel

10 Fifty mg of paclitaxel (Hauser chemicals), 95 mg of methoxypolyethylene glycol (MePEG) (molecular weight 350) (Union Carbide Inc.), 645mg of poly-L-lactic acid--MePEG diblock copolymer (Angiotech Pharmaceuticals, Vancouver Canada), 95 mg each of polycaprolactone- co-methoxypolyethylene glycol (each containing 17 units of ethylene glycol in the MePEG conjugated to either one unit of caprolactone (PCL1) or 5
15 units (PCL5) were weighed into a 20 ml glass vial and stirred at 50° C using a spatula for 5 to 10 minutes. The mixture formed a miscible composition in which all the drug was dissolved. The mixture was sucked up into a 1ml syringe through an 18 gauge needle and allowed to cool to room temperature.

20 The waxy material could be injected easily through a 21 gauge needle without compromising the integrity of the composition. When 100 µl of the mixture was injected into 5 ml of water and water acidified to pH 1, the mixture slowly dissolved and there was no precipitation of any of the components. The formulation self assembled into micelles.

Example 3

Injection of micellar formulation of paclitaxel along the perivascular margins of the carotid artery of a rat for the treatment of restenosis

Wistar rats weighing 400g to 500g were anesthetized with halothane. A vertical incision
30 was made over the trachea and the left external carotid artery was exposed. Connective tissue around the left common carotid artery was left untouched. Two ligatures were placed around the external carotid artery and an arteriotomy was made between them. A 2

French Fogarty balloon was introduced into the external carotid artery and pushed into the left common carotid artery and the balloon was inflated with saline. The balloon was passed up and down the entire length of the carotid artery three times to stretch the vessel and denude the endothelium. The balloon was removed and the ligatures tied off on the external carotid artery. A 3% paclitaxel loaded self-assembling micellar composition based on poly-L-lactic acid--MePEG blended with MePEG 350 in a 60/40 weight ratio (as described in Example 2A) was injected through a 24 G angiocatheter between a distal segment of the common carotid artery and the surrounding connective tissue. Typically, 0.1 to 0.2 ml of paste was applied around the artery in 4 injections in order to cover the whole circumference of the vessel on a length of approximately 1 cm. The wound was then closed and the animals recovered.

Using this method various doses of a polymeric dosage form of the antirestenosis compound paclitaxel was applied to the perivascular side of the damaged artery without the need for complete exposure of the artery (as in required for the application of a polymeric film to the artery). The rats tolerated this method of application well with no adverse effects noted in any animal. This example demonstrates a non-invasive method of applying a self assembly micellar formulation of paclitaxel. In this particular example some invasive surgery was used to apply the balloon catheter. However in humans the catheter would be applied from a distant location and it is envisaged that the paste would be applied to the damaged artery in humans via an angiocatheter without surgical exposure of the damaged artery. There was no evidence of toxicity from this method of injection and no sign of drug precipitation at the site of injection along the artery. At the end of two weeks the animals were examined for the presence of residual formulation or local toxicity indicative of non-biocompatible. In all animals treated there was no residual formulation at the site or any evidence of any toxicity in the animals. Clearly, the drug and polymer composition were dissolving and self assembling into a micellar formulation of the drug at the *in vivo* arterial site.

Example 4

Manufacture of a 10% paclitaxel loaded-self assembling micellar formulation of paclitaxel

Forty mg of paclitaxel (Hauser chemicals), 108 mg of methoxypolyethylene glycol (MePEG) (molecular weight 350) (Union Carbide Inc.) and 252 mg of poly-L-lactic acid-MePEG diblock copolymer (Angiotech Pharmaceuticals, Inc. Vancouver Canada) were
5 weighed into a 20 ml glass vial and stirred at 50° C using a spatula. The mixture formed a miscible composition in which all the drug was dissolved. The mixture was sucked up into a 1 ml syringe through an 18 gauge needle and allowed to cool to room temperature.

The waxy material could be injected easily through a 21 gauge needle without
10 compromise of the integrity of the composition. When 100 µl of the mixture was injected into 5 ml of water the mixture slowly dissolved. There was no precipitation of any of the components. The formulation self assembled into micelles.

Although the foregoing invention has been described in some detail by way of
15 illustration and example for purposes of clarity of understanding, it will be readily apparent to those of skill in the art in light of the teachings of this invention that changes and modification may be made thereto without departing from the spirit or scope of the appended claims. All patents, patent applications and publications referred to herein are hereby incorporated by reference.

WE CLAIM:

1. A micelle forming composition comprising:
 - (a) one or more hydrophobic drugs;
 - 5 (b) one or more biocompatible, micelle forming polymers; and,
 - (c) one or more biocompatible, low molecular weight, water soluble polymers,wherein the one or more water soluble polymers are present in an amount sufficient that the composition is injectable.
- 10 2. The composition of claim 1, wherein the composition is substantially free of non-polymeric organic solvent.
3. The composition of claim 1 or 2, wherein the one or more micelle forming
15 polymers comprises a block copolymer.
4. The composition of claim 3, wherein the block copolymer comprises a hydrophobic portion comprising a polymer block selected from the group consisting of: a polyester and a polyanhydride.
- 20 5. The composition of claim 4, wherein the polymer block is selected from the group consisting of: polyglycolic acid, polybutyrolactone, polyhydroxybutyrate, polylactic acid and polylacapolactone.
- 25 6. The composition of claim 4 or 5, wherein the hydrophobic portion is a polymer having a molecular weight of about 200 to about 500.
7. The composition of any one of claims 3-6, wherein the block copolymer
30 comprises a hydrophilic portion that is a polyethylene oxide.

8. The composition of claim 7, wherein the polyethylene oxide is selected from the group consisting of polyethylene glycol (PEG) and methoxypolyethylene glycol (MePEG).

5 9. The composition of claim 7 or 8, wherein the hydrophilic portion is a polymer having a molecular weight of at least 750.

10. The composition of claim 9, wherein the molecular weight is less than about 8000.

10

11. The composition of claim 9, wherein the molecular weight is from about 1000 to about 5000.

12. The composition of claim 9, wherein the molecular weight is from about 1000 to about 3000.

15

13. The composition of claim 9, wherein the molecular weight is from about 1000 to about 2000.

20 14. The composition of claim 9, wherein the molecular weight is about 2000.

15. The composition of any one of claims 1-14, wherein the water soluble polymer is selected from the group consisting of: a polyethylene oxide, low molecular weight polylactic acid, low molecular weight polyglycolic acid and a pluronic, wherein the water soluble polymer is a liquid or semi-solid at room temperature.

25

16. The composition of any claim 15, wherein the water soluble polymer is a polyethylene oxide.

30

17. The composition of claim 16, wherein the polyethylene oxide is selected from the group consisting of PEG and MePEG.

18. The composition of claim 16 or 17, wherein the polyethylene oxide has a molecular weight of about 1000 or less.

5 19. A device for injection of a substance into the body of a patient wherein the device comprises a composition of any one of claims 1-18 for injection.

20. The device of claim 19, wherein the device is a syringe.

10 21. The device of claim 20, wherein the syringe further comprises a needle cannula.

22. A method of forming micelles comprising a hydrophobic drug wherein a composition according to any one of claims 1-17 is placed into an aqueous media.

15

23. The method of claim 22, wherein said placing is by injection into a site in a patient's body and micelles are formed at the site.

24. The use of a composition according to any one of claims 1-17 for
20 administration to a patient to form hydrophobic drug containing micelles within the body of the patient.

25. The use of claim 24, wherein the administration is by injection to a site within the patient's body and the micelles form at the site.

25

26. A micelle forming composition comprising:

- (a) one or more hydrophobic drugs;
- (b) one or more biocompatible, micelle forming polymers; and,
- (c) one or more biocompatible, low molecular weight, water soluble
30 polymers,

wherein the micelle forming polymer is a block copolymer comprising a hydrophobic and a hydrophilic portion, the hydrophobic portion comprising a

polymer block selected from the group consisting of: a polyester and a polyanhydride; and, the hydrophilic portion is a polyethylene oxide having a molecular weight of about 750 or more.

5 27. The composition of claim 26, wherein the hydrophobic portion comprises a polymer block selected from the group consisting of: polyglycolic acid, polybutyrolactone, polyhydroxybutyrate, polylactic acid and polylacapolactone.

28. The composition of claim 26 or 27, wherein the hydrophobic portion is a
10 polymer having a molecular weight of about 200 to about 500.

29. The composition of any one of claims 26-28, wherein the water soluble polymer is a water soluble, low molecular weight, polylactic or polyglycolic acid; a water soluble pluronic polymer; or, a polyethylene oxide, wherein the water soluble
15 polymer is a liquid or semi-solid at room temperature.

30. The composition of claim 29, wherein the water soluble polymer is a polyethylene oxide having a molecular weight of about 1000 or less selected from the group consisting of PEG and MePEG.
20

31. The composition of any one of claims 26-30, wherein the amount of water soluble polymer in the composition is sufficient for the composition to be injectable.

32. The composition of any one of claims 26-31, wherein the composition is
25 substantially free of organic solvent.

33. A composition according to any one of claims 26-32, wherein the composition is capable of forming micelles in aqueous medium at a critical micelle concentration (CMC) of about 500 μ M or less.
30

34. The composition according to claim 33, wherein the CMC is about 100 μ M or less.

35. The composition according to claim 33, wherein the CMC is about 50 μ M or less.

5 36. A method of forming micelles comprising a hydrophobic drug, wherein a composition according to any one of claims 26-35 is placed in an aqueous media whereby micelles comprising the hydrophobic drug are formed therein.

37. The method of claim 36, wherein said placing is *in vitro*.

10

38. The method of claim 36, wherein said placing is *in vivo*.

39. The use of a composition according to any one of claims 26-35, for forming hydrophobic drug containing micelles *in vivo*.

15

40. The use of a composition according to any one of claims 26-35 for preparation of a medicament for administration to a patient.

20

1/1

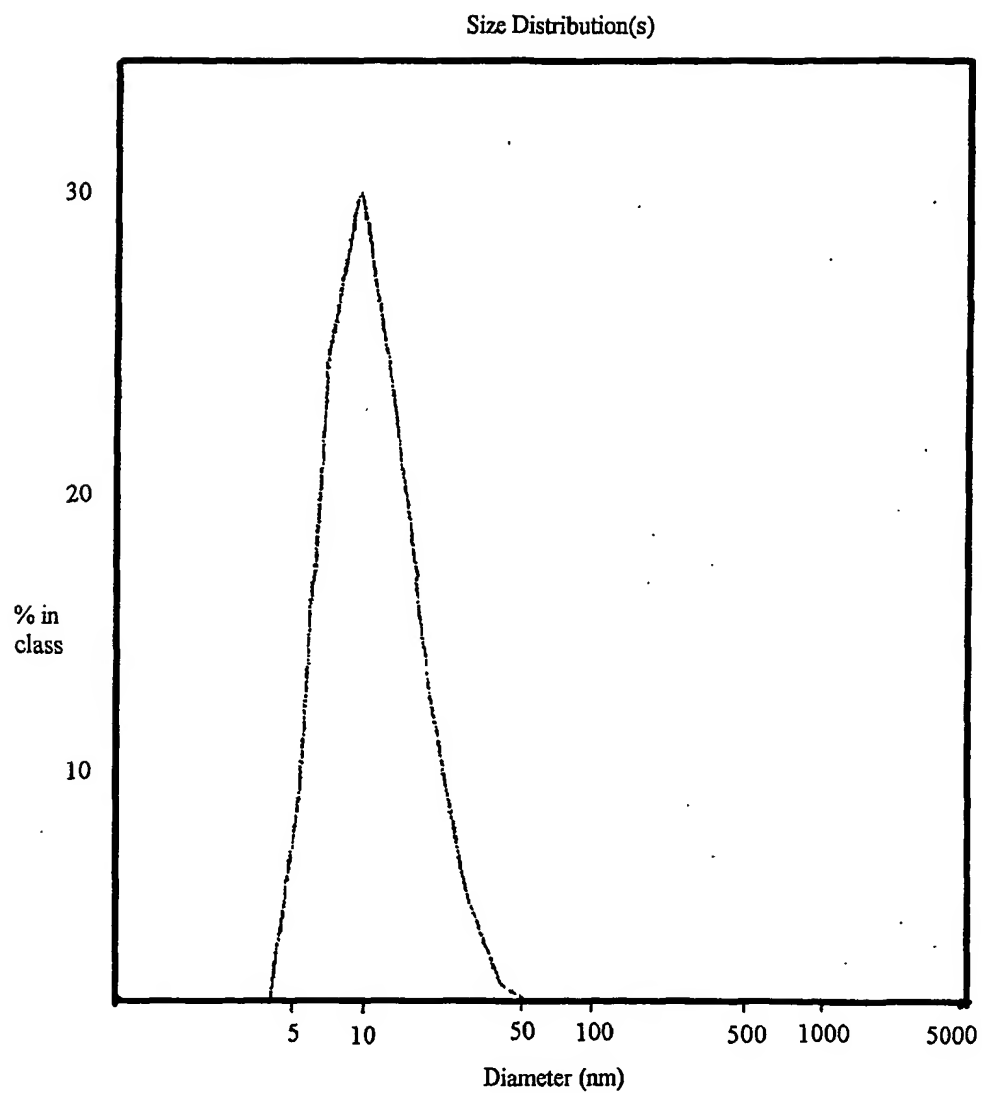


Figure 1

INTERNATIONAL SEARCH REPORT

 Int. Application No
 PCT/CA 02/00542

 A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61K9/51

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

 Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | US 6 136 846 A (GORE ASHOK Y ET AL) 24 October 2000 (2000-10-24) cited in the application column 3, line 15 - line 32 --- | 1-3 |
| X | WO 98 07434 A (SUPRATEK PHARMA INC ;ALAKHOV VALERY Y (CA); KABANOV ALEXANDER V (U) 26 February 1998 (1998-02-26) page 5, line 20 - line 21 example 1 --- | 1-3,6-25 |
| X | WO 99 21908 A (ANGIOTECH PHARM INC ;UNIV BRITISH COLUMBIA (CA); BURT HELEN M (CA)) 6 May 1999 (1999-05-06) cited in the application page 7, line 29 -page 8, line 29 page 14, line 8 - line 17 examples --- -/-- | 1-40 |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the International filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the International filing date but later than the priority date claimed

- "T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the International search

11 September 2002

Date of mailing of the International search report

30/09/2002

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INTERNATIONAL SEARCH REPORT

Int Application No

PCT/CA 02/00542

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | WO 01 12718 A (SEO MIN HYU ;CHOI IN JA (KR); SAMYANG CORP (KR)) 22 February 2001 (2001-02-22) page 3, paragraph 4 -page 4, paragraph 1 page 5, paragraph 2 -page 8, paragraph 2 examples | 1-40 |
| P,X | WO 01 85216 A (SEO MIN HYU ;SAMYANG CORP (KR); YI YIL WOONG (KR); YU JAE WON (KR)) 15 November 2001 (2001-11-15) page 5, line 22 -page 6, line 17 examples | 1-40 |
| A | WO 99 43343 A (SUPRATEK PHARMA INC ;ALKHOV VALERY Y (CA); KABANOV ALEXANDER V (US) 2 September 1999 (1999-09-02) page 4, line 20 -page 5, line 22 page 29, line 3 - line 5 | 1-3,6-25 |
| A | ZHANG X., JACKSON J.K. ET AL.: "Development of amphiphilic diblock copolymers as micellar carriers of taxol" INT. J. PHARMACEUTICS, vol. 132, 1996, pages 195-206, XP002213203 cited in the application the whole document | 1-40 |

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 23-25, 38, 39
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/CA 02 00542

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 23-25, 38 and 39 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: 23-25, 38, 39

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Application No

PCT/CA 02/00542

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
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